

Naturally Occurring Rearranged Taxoids^{1,*}

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Abstract

The rearranged taxoids have recently been reported from different *Taxus* species. The literature concerning the chemistry, biogenesis, and bioactivity of such compounds is reviewed.

Key words

Rearranged taxoids, 11(15→1)-abeotaxoids, 2(3→20)-abeotaxoids, chemistry, biogenesis, bioactivity.

Introduction

Taxol (1) (1), a complex diterpenoid alkaloid, isolated originally from the pacific yew, *Taxus brevifolia* (Taxaceae) has emerged as a highly promising cancer chemotherapeutic agent. Its clinical activity against a broad spectrum of cancerous disease, such as refractory human ovarian, melanoma, and breast cancers (2–5) has spurred a worldwide search (6) for better sources and improved analogues of this compound. During the isolation of novel taxoids from different yew plants (*Taxus* species), some compounds have been observed with rearranged skeletons. These compounds represent a novel and rapidly growing group of taxoids. Here we review the chemistry, biogenesis, and bioactivity of the naturally occurring, rearranged taxoids.

Chemistry

Normal taxoids contain a 6/8/6-membered ring system (A), but the rearranged taxoids possess a 5/7/6- or a 6/10/6-membered ring system (B and C, respectively). Taxoids with the B ring system are known as 11(15→1)-abeotaxoids (7–9) or A-nortaxoids (10) and those with C ring system as 2(3→20)-abeotaxoids (11). They have been isolated from the bark, stems, needles, and seeds of several *Taxus* species. The reported naturally occurring rearranged taxoids and their physical properties are presented in Table 1.

Most rearranged taxoids contain the 11(15→1)-abeotaxane skeleton (B) (7, 16, 8, 9) which was first observed (7) in a semisynthetic product from taxol (1). Brevifoliol (2), originally isolated (12, 13) from *T. brevifolia*, was the first natural taxoid isolated possessing this skeleton. It was initially considered (12, 13) to be a normal taxoid, and later proved (16, 8, 9) to be an 11(15→1)-abeotaxoid 2 after reinterpretation of its NMR spectra (mainly HMBC and ¹³C-NMR) and by X-ray crystallographic analysis. Brevifoliol is the most abundant rearranged taxoid in the needles of *T. brevifolia* throughout most of the year (14). Taxchinin B (16) (20) isolated, from *T. chinensis*, was the first 11(15→1)-abeotaxoid isolated with an oxetane ring.

Thirteen derivatives of brevifoliol (3–15) and eleven derivatives of taxchinin B (17–27) have been isolated and characterised from different yew plants (Table 1). Many compounds (3–7 and 17–20) were initially reported to have the normal taxoid skeleton but were later revised to 11(15→1)-abeotaxoids (references in the Table). In CDCl₃ solution the taxoids possessing a brevifoliol skeleton show conformational isomerisation (15, 8, 10, 23) which appears to be characteristic of this structural type. Besides the derivatives of brevifoliol and taxchinin B, three other novel 11(15→1)-abeotaxoids, wallifoliol (28) (17), taxuchin A (29) (29), and yunantaxusin A (30) (30) have been isolated. The former is the only taxoid, reported so far, which possesses the 5/6/6/6/4-membered ring system. Taxuchin A contains an epoxy ring at C-4. In yunantaxusin A the oxetane ring is open.

Four rearranged taxoids have been found with the 2 (3→20)-abeotaxane skeleton (Table 1). Taxine A (31) (31, 32), the first compound of this group, was characterised by single crystal X-ray diffractometry. The structures of its three derivatives, 32–34, were elucidated (11, 24, 33) by spectroscopic analysis and by comparison of the spectral data with those of taxine A (31).

Biogenesis

Taxoids and rearranged taxoids arise by two different biogenetic pathways (Scheme 1) (29, 11) starting from a common precursor **a**. The generation of the 5- or 6-membered A-ring depends on the mode of ring closure for **b**. The formation of a 5-membered A-ring and

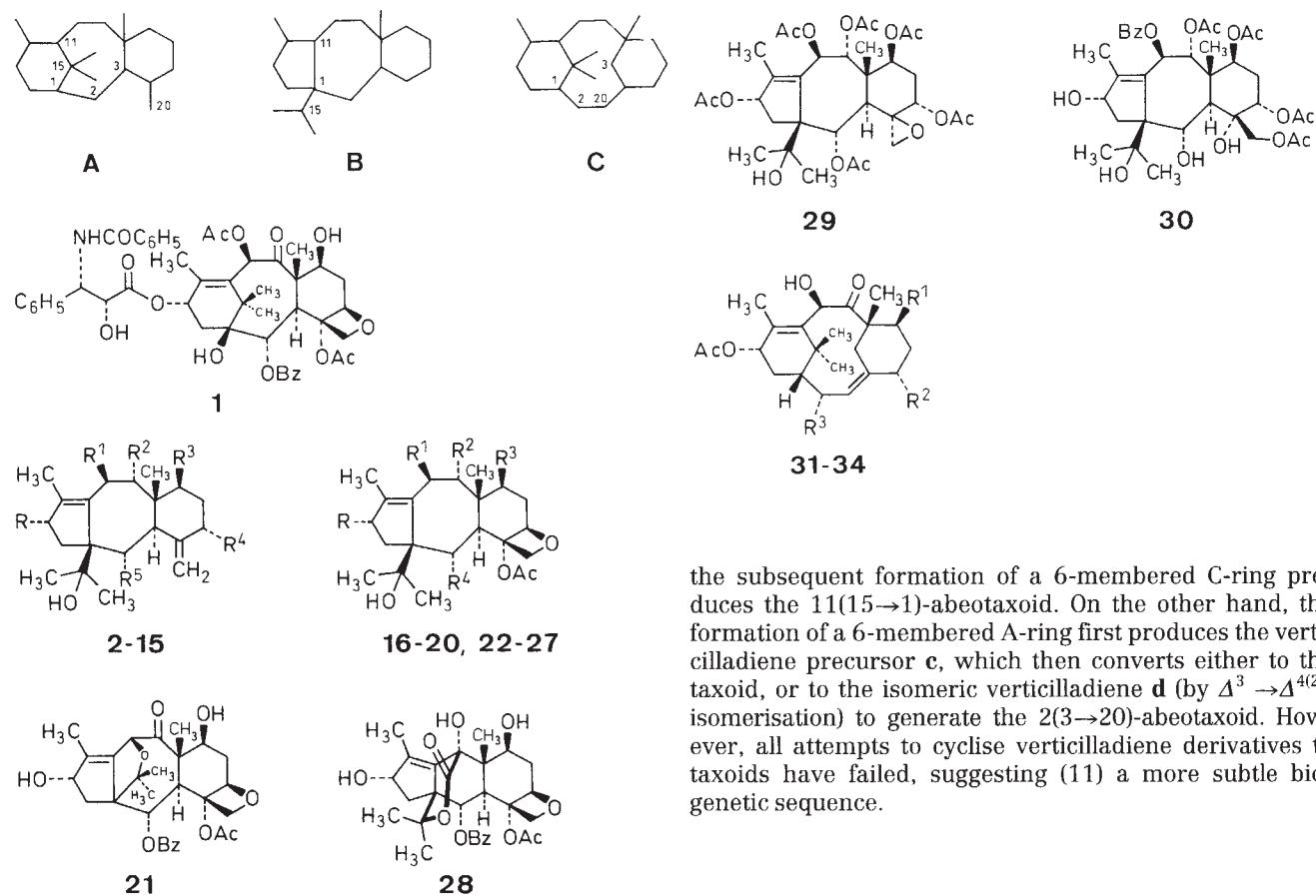
Table 1 Naturally occurring rearranged taxoids

Name, Structure	Mol. formula; M.p. (solvent); [α] _D (solvent)	Source
1. 11(15→1)-abeotaxoids		
A. <i>Brevifoliol and its derivatives</i>		
i. Brevifoliol (2) ($R = R^4 = OH$, $R^1 = OBz$, $R^2 = R^3 = OAc$, $R^5 = H$)	$C_{31}H_{40}O_9$; 200–203 °C (<i>n</i> -C ₆ H ₁₄ -Me ₂ CO) (12), 200–205 °C (<i>n</i> -C ₆ H ₁₄ -Me ₂ CO) (13), 200–202 °C (<i>n</i> -C ₆ H ₁₄ -Me ₂ CO) (15); –28.0° (CHCl ₃) (13), –24.0° (CHCl ₃) (15)	<i>T. brevifolia</i> Nutt. (needles, stem bark and twigs) (12,13,9,14) <i>T. wallichiana</i> Zucc. (needles) (15,16,8,17) <i>T. baccata</i> Linn. (twigs) (18)
ii. Taxchinin A (3) ($R = R^4 = OH$, $R^1 = OBz$, $R^2 = R^3 = R^5 = OAc$)	$C_{33}H_{42}O_{11}$; 208–210 °C (Et ₂ O) (19,20), 198 °C (Me ₂ CO-Et ₂ O) (21); –34.62° (CH ₂ Cl ₂) (20), –24.0° (CH ₂ Cl ₂) (21)	<i>T. chinensis</i> (Pilg.) Rehd. (stems and needles) (19,20)
iii. 13-Acetyl brevifoliol (4) ($R = R^2 = R^3 = OAc$, $R^1 = OBz$, $R^4 = OH$, $R^5 = H$)	$C_{33}H_{42}O_{10}$; thick oil (15); +8.0° (MeOH) (15), –26.0° (CHCl ₃) (9)	<i>T. baccata</i> Linn. (seeds) (21,8)
iv. –* (5) ($R = R^1 = R^4 = OH$, $R^2 = OAc$, $R^3 = R^5 = H$)	$C_{22}H_{34}O_6$; 160–162 °C (<i>n</i> -C ₆ H ₁₄ -AcOMe) (15); –24.0° (MeOH) (15)	<i>T. wallichiana</i> Zucc. (needles) (15,8)
v. –* (6) ($R = R^1 = R^4 = OH$, $R^2 = R^3 = OAc$, $R^5 = H$)	$C_{24}H_{36}O_8$; non-cryst. (15); –5.0° (MeOH) (15)	<i>T. brevifolia</i> Nutt. (needles) (9)
vi. –* (7) ($R = R^1 = R^4 = OH$, $R^2 = R^5 = OAc$, $R^3 = H$)	$C_{24}H_{36}O_8$; 154 °C (22); –22.0° (CHCl ₃) (22)	<i>T. baccata</i> Linn. (needles) (22,8)
vii. Taxchinin D (8) ($R = R^2 = R^3 = R^5 = OAc$, $R^1 = OBz$, $R^4 = OH$)	$C_{35}H_{40}O_{12}$; 138–141 °C (<i>n</i> -C ₆ H ₁₄ -Me ₂ CO);	<i>T. chinensis</i> (Pilg.) Rehd. (stems and needles) (23)
viii. Taxchinin G (9) ($R = R^2 = R^3 = R^5 = OAc$, $R^1 = R^4 = OH$)	$C_{28}H_{35}O_{11}$; 140–143 °C (Et ₂ O)	Same as for 8
ix. 9-Deacetyl-9-benzoyl-10-debenzoyl-brevifoliol (10) ($R = R^1 = R^4 = OH$, $R^2 = OBz$, $R^3 = OAc$, $R^5 = H$)	$C_{29}H_{38}O_8$; 152 °C; +18.0° (CHCl ₃)	<i>T. brevifolia</i> Nutt. (bark) (10)
x. 10 β -Benzoxo-1 β -hydroxy-5 α -(3'-dimethylamino-3'-phenyl)-propanoxy-1 β -hydroxy-7 β , 9 α , 13 α -triacetoxyl-11(15→1)-abeotaxa-4(20), 11-deine (11) ($R = R^2 = R^3 = OAc$, $R^1 = OBz$, $R^4 = OCOCH2C(\alpha-NMe2)(\beta-H)Ph$, $R^5 = H$)	$C_{44}H_{55}O_{11}N$; Amorphous; –7.0° (CHCl ₃)	<i>T. brevifolia</i> Nutt. (needles) (9)
xi. 10 β -Benzoxo-1 β -hydroxy-5 α -(3'-methylamino-3'-phenyl)propanoxy-7 β , 9 α , 13 α -triacetoxyl-11(15→1)-abeotaxa-4(20), 11-deine (12) [$R = R^2 = R^3 = OAc$, $R^1 = OBz$, $R^4 = OCOCH2C(\alpha-NHMe)(\beta-H)Ph$, $R^5 = H$]	$C_{43}H_{53}O_{11}N$; Amorphous; –7.0° (CHCl ₃)	Same as for 11
xii. 10 β -Benzoxo-5 α -cinnamoxyl-1 β -hydroxy-7 β , 9 α , 13 α -triacetoxyl-11(15→1)-abeotaxa-4(20), 11-deine (Taxuspine A) (13) ($R = R^2 = R^3 = OAc$, $R^1 = OBz$, $R^4 = trans$ -PhCH = CHOCO, $R^5 = H$)	$C_{42}H_{46}O_{11}$; Amorphous (24); –26.0° (CHCl ₃) (9), –3.4° (CHCl ₃) (24)	Same as for 11 and <i>T. cuspidata</i> Sieb. et Zucc. (stems) (24)
xiii. Taxchinin E (14) ($R = trans$ -PhCH = CHOCO, $R^1 = OBz$, $R^2 = R^3 = R^5 = OAc$, $R^4 = OH$)	$C_{42}H_{48}O_{12}$; 134–136 °C; –17.49° (CHCl ₃)	<i>T. chinensis</i> (Pilg.) Rehd. (stems and needles) (25)
xiv. Taxchinin H (15) ($R = OH$, $R^1 = OBz$, $R^2 = R^3 = OAc$, $R^4 = trans$ -PhCH = CHOCO-, $R^5 = H$)	$C_{40}H_{46}O_{10}$; 115–118 °C; –65.29° (CHCl ₃)	Same as for 14
B. <i>Taxchinin B and its derivatives</i>		
xv. Taxchinin B (16) ($R = trans$ -PhCH = CHOCO, $R^1 = OBz$, $R^2 = R^3 = R^4 = OAc$)	$C_{44}H_{48}O_{13}$; 176–178 °C (MeOH); +7.40° (CHCl ₃)	<i>T. chinensis</i> (Pilg.) Rehd. (stems and needles) (20)
xvi. 13-Decinnamoyltaxchinin B (17) ($R = OH$, $R^1 = OBz$, $R^2 = R^3 = R^4 = OAc$)	$C_{35}H_{44}O_{13}$; 225–226 °C (<i>n</i> -C ₆ H ₁₄ -AcOMe) (15), 227–228 °C (<i>n</i> -C ₆ H ₁₄ -Me ₂ CO) (26); –38.0° (MeOH) (15), –40.0° (MeOH) (26)	<i>T. wallichiana</i> Zucc. (needles) (15,8) <i>T. baccata</i> Linn. (twigs and needles) (18,26)
xvii. Taxchinin C (18) ($R = R^3 = OAc$, $R^1 = R^2 = R^4 = OBz$)	$C_{47}H_{50}O_{14}$; 212–214 °C (<i>n</i> -C ₆ H ₁₄ -Me ₂ CO) (20), Amorphous (27); –45.6° (CH ₂ Cl ₂) (20)	<i>T. chinensis</i> (Pilg.) Rehd. (stems and needles) (20), <i>T. brevifolia</i> Nutt. (bark) (27,9)
xviii. –* (19) ($R = R^2 = R^3 = OAc$, $R^1 = R^4 = OBz$)	$C_{42}H_{48}O_{14}$; Amorphous (27); –	<i>T. brevifolia</i> Nutt. (bark) (27,9)
xix. –* (20) ($R = R^1 = R^2 = OAc$, $R^3 = R^4 = OBz$)	$C_{42}H_{48}O_{14}$; Amorphous (27); –	Same as for 19
xx. 10,15-Epoxy-11(15→1)-abeo-10-deacetyl/baccatin III (21)	$C_{29}H_{34}O_9$; Oil; –18.0° (CH ₂ Cl ₂)	<i>T. wallichiana</i> Zucc. (needles) (28)
xxi. 7,9,10-Trideacetylabeobaccatin VI (22) ($R = OAc$, $R^1 = R^2 = R^3 = OH$, $R^4 = OBz$)	$C_{31}H_{40}O_{11}$; Powder; –26.0° (CHCl ₃)	<i>T. baccata</i> Linn. (twigs and needles) (11)
xxii. 7,13-Dideacetyl-9,10-debenzoyl-taxchinin C (23) ($R = R^1 = R^2 = R^3 = OH$, $R^4 = OBz$)	$C_{29}H_{38}O_{10}$; 162 °C; –15.0° (CHCl ₃)	<i>T. brevifolia</i> Nutt. (bark) (10)

Table 1 Continued

Name, Structure	Mol. formula; M.p. (solvent); [α] _D (solvent)	Source
xviii. 13-Acetyl-13-decinnamoyltaxchinin B (24) ($R = R^2 = R^3 = R^4 = OAc$, $R^1 = OBz$)	$C_{37}H_{46}O_{14}$; 243–244 °C (nC_6H_{14} –Me ₂ CO); –54.0° (CHCl ₃)	<i>T. baccata</i> Linn. (needles) (26)
xix. Taxchinin I (25) ($R = R^3 = OAc$, $R^1 = OH$, $R^2 = R^4 = OBz$)	$C_{40}H_{46}O_{13}$; 235–237 °C (Et ₂ O); –6.08° (CHCl ₃)	<i>T. chinensis</i> (Pilg) Rehd. (stems and needles) (25)
xv. Taxchinin J (26) ($R = trans$ -PhCH = CHOCO, $R^1 = OH$, $R^2 = OBz$, $R^3 =$ $R^4 = OAc$)	$C_{42}H_{48}O_{13}$; 238–240 °C (Et ₂ O); +23.36° (CHCl ₃)	Same as for 25
xvi. Taxchinin K (27) ($R = R^3 = R^4 = OAc$, $R^1 = R^2 = OBz$)	$C_{42}H_{48}O_{14}$; 217–219 °C (nC_6H_{14} –Et ₂ O); –30.0° (CHCl ₃)	Same as for 25
C. Other		
xxvii. Wallifoliol (28)	$C_{29}H_{34}O_{10}$; Amorphous; –10.8° (MeOH)	<i>T. wallichiana</i> Zucc. (needles) (17)
xxviii. Taxchin A (29)	$C_{32}H_{44}O_{14}$; 248–250 °C (Et ₂ O); –64.8° (MeOH)	<i>T. chinensis</i> (Pilg) Rehd. (bark) (29)
xxix. Yunantaxusin A (30)	$C_{35}H_{46}O_{14}$; 239–240 °C (Me ₂ CO); –52.0° (MeOH)	<i>T. yunnanensis</i> Cheng et L.K. Fu (stems and needles) (30)
2(3→20)-abeotaxoids		
xxx. Taxine A (31) ($R^1 = OH$, $R^2 =$ OCOC(α -OH)(β -H) C(α -NMe ₂)(β -H)Ph, $R^3 = OAc$)	$C_{35}H_{47}NO_{10}$; 204–206 °C (Et ₂ O); –140.0° (CHCl ₃)	<i>T. baccata</i> Linn. (needles) (31,32)
xxxi. Deaminooacyltaxin A (32) ($R^1 = R^2 = OH$, $R^3 = OAc$)	$C_{24}H_{34}O_8$; Gum; –	<i>T. baccata</i> Linn. (needles and twigs) (11)
xxxii. Taxuspine B (33) ($R^1 = R^3 = OAc$, $R^2 = trans$ -PhCH = CHOCO)	$C_{35}H_{42}O_{10}$; Amorphous; –40.6° (CHCl ₃)	<i>T. cuspidata</i> Sieb et Zucc. (stems) (24)
xxxiii. 2-Deacetyltaxin A (34) [$R^1 = R^3 = OH$, $R^2 = OCOC$ (α -OH)(β -H) C(α -NMe ₂)(β -H)Ph]	$C_{33}H_{45}NO_9$; Amorphous; –106.0° (CHCl ₃)	<i>T. baccata</i> Linn. (needles) (33)

*Originally proposed names based on the taxane skeleton were proved to be incorrect after revision of the structure.



Bioactivity

The biological activities of some naturally occurring rearranged taxoids have been studied. The synthetic 15-hydroxy-11(15 \rightarrow 1)-abeotaxol derivatives showed a tubulin-binding activity (7, 34) but no *in vitro* cytotoxicity (7). This result created interest in the biological evaluation of the natural rearranged taxoids. Brevifoliol (2) itself showed no activity in tubulin assays (16). Brevifoliol-13[N-benzoyl-(2R',3'S)-3'-phenylisoserinate] (35) in which the C-13 side chain of taxol has been attached to brevifoliol (2) was also found to be inactive in the microtubule binding assay and to have little cytotoxicity against B 16 melanoma cells. Taxchinins A (3), B (16), and C (18) had little effect on the microtubule binding assembly ($ID_{50} > 100 \mu\text{M}$) (19, 20) compared to that of taxol ($ID_{50} = 0.29 \mu\text{M}$).

The cytotoxicity of taxuspine A and B was evaluated (24) against murine lymphoma L 1210 and

human epidermoid carcinoma KB cells. Taxuspine A (13) exhibited modest cytotoxicity against L 1210 cells ($IC_{50} = 4.2 \mu\text{g/ml}$) and taxuspine B (33) showed a weak cytotoxicity ($IC_{50} = 18 \mu\text{g/ml}$) although taxol (1) was found to be the most cytotoxic ($IC_{50} = 0.33 \mu\text{g/ml}$) under the experimental conditions. Taxuspine B (33) exhibited (24) appreciable taxol-like activity to reduce CaCl_2 -induced depolymerisation of microtubules (36, 37). This compound also increased (24) the vincristine accumulation in multidrug-resistant tumour cells; it is as potent as verapamil (38, 39) and so may be useful for overcoming multidrug-resistance in tumour cells.

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Scheme 1 Biogenetic pathways to taxoids and rearranged taxoids.

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